General

Guideline Title

WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia.

Bibliographic Source(s)

World Health Organization (WHO). WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia. Geneva (Switzerland): World Health Organization (WHO); 2011. 38 p. [34 references]

Guideline Status

This is the current release of the guideline.

Recommendations

Major Recommendations

The rating schemes for the quality of the evidence (very low, low, moderate, high) and the strength of the recommendations (weak, strong) are defined at the end of the "Major Recommendations" field.

Rest for Prevention and Treatment of Pre-eclampsia

Recommendations

1. Advice to rest at home is not recommended as an intervention for the primary prevention of pre-eclampsia and hypertensive disorders of pregnancy in women considered to be at risk of developing those conditions. (Low-quality evidence, Weak recommendation)
2. Strict bedrest is not recommended for improving pregnancy outcomes in women with hypertension (with or without proteinuria) in pregnancy. (Low-quality evidence, Weak recommendation)

Remarks

a. The guideline development group acknowledged that there may be situations in which different levels of rest, either at home or in hospital, may be indicated for individual women. The above recommendations do not cover advice regarding overall physical activity and manual or office work.
b. Women may need to be hospitalized for reasons other than bedrest, such as for maternal and fetal surveillance. The guideline development group agreed that hospitalization for maternal and fetal surveillance is resource intensive and should be considered as a priority for research and future recommendations.

Dietary Salt Restriction for Prevention of Pre-eclampsia

Recommendation

3. Restriction in dietary salt intake during pregnancy with the aim of preventing the development of pre-eclampsia and its complications is not recommended. (Moderate-quality evidence, Weak recommendation)

Remarks

a. The guideline development group agreed that healthy dietary practices should be promoted in the general population, including among pregnant women.
b. The group considered the avoidance of excessive dietary salt intake as a healthy dietary practice.

Calcium Supplementation during Pregnancy to Prevent Pre-eclampsia and Its Complications

Recommendation

4. In areas where dietary calcium intake is low, calcium supplementation during pregnancy (at doses of 1.5–2.0 g elemental calcium/day) is recommended for the prevention of pre-eclampsia in all women, but especially in those at high risk of developing pre-eclampsia. (Moderate-quality evidence, Strong recommendation)

Remarks

a. The guideline development group agreed that healthy dietary practices should be promoted in the general population, among pregnant women.
b. The group considered appropriate dietary calcium intake as a healthy dietary practice. Available evidence supports the theory that calcium supplementation reduces the risk of development of pre-eclampsia by filling a dietary gap in calcium intake; calcium supplementation does not act as a therapeutic agent. In some populations, barriers to increasing dietary calcium intake may be greater than those against providing calcium supplementation to pregnant women. The guideline development group noted that determining the dietary calcium intake on an individual basis is complex. In this context, the guideline group targeted this recommendation at populations living in geographical areas where low dietary calcium intake is commonly observed.
c. Women are regarded as being at high risk of developing pre-eclampsia if they have one or more of the following risk factors: previous pre-eclampsia; diabetes; chronic hypertension; renal disease; autoimmune disease; and multiple pregnancies. This is not an exhaustive list, but can be adapted/complemented based on the local epidemiology of pre-eclampsia.
d. The guideline development group considered that in populations with adequate calcium intake, additional calcium supplementation does not improve outcomes related to pre-eclampsia and hypertensive disorders of pregnancy.
e. The group also considered the issue of interaction between iron supplements and calcium supplements. In this regard the group noted that concomitant administration of the two should be avoided. Ideally, the two supplements should be administered several hours apart (e.g., morning and evening). With regard to the timing of initiation of calcium supplementation, in most of the trials included in the Cochrane review it was started around 20 weeks of gestation.
f. Additional questions related to calcium and other pregnancy-related complications will be addressed by the WHO Nutrition Guidance Expert Advisory Group (NUGAG).

Note

One participant in the guideline development group wished to record his dissent with the above recommendation. He believed that, while the current evidence supports the view that calcium supplementation in women from populations with low intake of calcium reduces the risk of diagnosis of pre-eclampsia, in these women calcium may function as an antihypertensive agent, reducing the incidence of hypertension and, because of that, the diagnosis of 'pre-eclampsia' (i.e., proteinuric hypertension in pregnancy). In other words, he was concerned that calcium supplementation could mask the development of pre-eclampsia. He was also concerned that the antihypertensive effect of calcium would not reduce the incidence of complications of pre-eclampsia if 'heavy proteinuria' is excluded from the diagnosis of 'severe pre-eclampsia'.

Vitamin D Supplementation

Recommendation

5. Vitamin D supplementation during pregnancy is not recommended to prevent the development of pre-eclampsia and its complications. (Very-low-quality evidence, Strong recommendation)

Remark

a. The guideline development group noted that several studies were still in progress on this topic which may change the evidence base in the future. The group was concerned about the limited evidence on safety of vitamin D supplementation during pregnancy and therefore made a strong recommendation against the use of vitamin D supplementation for prevention of pre-eclampsia during pregnancy.

Antioxidants for Prevention of Pre-eclampsia and Its Complications

Recommendation

6. Individual or combined vitamin C and vitamin E supplementation during pregnancy is not recommended to prevent the development of pre-eclampsia and its complications. (High-quality evidence, Strong recommendation)

Antiplatelets for Prevention of Pre-eclampsia

Recommendations

7. Low-dose acetylsalicylic acid (aspirin, 75 mg/day) is recommended for the prevention of pre-eclampsia in women at high risk of developing the condition. (Moderate-quality evidence, Strong recommendation)
8. Low-dose acetylsalicylic acid (aspirin, 75 mg/day) for the prevention of pre-eclampsia and its related complications should be initiated before 20 weeks of pregnancy. (Low-quality evidence, Weak recommendation)

Remarks

a. Women are regarded as being at high risk of developing pre-eclampsia if they have one or more of the following risk factors: previous pre-eclampsia; diabetes; chronic hypertension; renal disease; autoimmune disease; and multiple pregnancies. This is not an exhaustive list, but can be adapted/complemented based on the local epidemiology of pre-eclampsia.
b. The guideline development group acknowledged that in settings where 75 mg aspirin tablets are not available, the available dose nearest to 75 mg should be used.
c. While low-dose aspirin has been shown to be beneficial in women at high risk of pre-eclampsia, there is a paucity of evidence to suggest that any subset of women within the high-risk group would benefit from aspirin therapy.
d. The guideline development group noted that it may be appropriate to initiate antiplatelet agents before 20 weeks of gestation, and, if possible, as early as 12 weeks of gestation.

Antihypertensive Drugs and Diuretics

Recommendations

9. Women with severe hypertension during pregnancy should receive treatment with antihypertensive drugs. (Very-low-quality evidence, Strong recommendation)
10. The choice and route of administration of an antihypertensive drug for severe hypertension during pregnancy, in preference to others, should be based primarily on the prescribing clinician's experience with that particular drug, its cost and local availability. (Very-low-quality evidence, Weak recommendation)
11. Diuretics, particularly thiazides, are not recommended for the prevention of pre-eclampsia and its complications. (Low-quality evidence, Strong recommendation)

Remarks

a. The guideline development group considered that there is absence of clinical uncertainty over whether treatment of severe hypertension during pregnancy is beneficial. This recommendation was made based on expert opinion; the group considered that most maternal deaths related to hypertensive disorders are associated with complications of uncontrolled severe high blood pressure. Based on that, the group agreed that antihypertensive treatment should be recommended in all cases of severe acute hypertension.
b. With regard to the treatment of mild/moderate hypertension in pre-eclampsia, a formal evidence review was conducted. The guideline development group considered the available evidence controversial, as there are potential harms and benefits associated with both lines of action. The group was aware of ongoing trials that might provide more robust data in the near future for guidance. Hence, they decided not to issue a recommendation on the treatment of mild/moderate hypertension until further evidence becomes available.
c. In terms of the choice and route of administration of an antihypertensive drug for severe hypertension during pregnancy, the guideline development group noted that not only is the evidence base for this recommendation limited, but also some antihypertensive drugs may not be feasible options in many settings. The group acknowledged that hydralazine, alpha methyldopa, beta blockers (including labetalol) and nifedipine have been extensively used, and therefore, these agents would seem to be reasonable choices until further evidence becomes available. The group noted that there was no evidence to suggest that nifedipine interacts adversely with magnesium sulfate. In addition, the

group considered that the use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and sodium nitroprusside should be avoided due to safety concerns.

d. In not recommending diuretics, particularly thiazides, for the for the prevention of pre-eclampsia and its complications, the group noted that this recommendation applies only to women at risk of developing pre-eclampsia who are not currently under treatment with diuretics. It does not apply to the use of diuretics for non-pre-eclampsia-related indications.

Magnesium Sulfate for Prevention and Treatment of Eclampsia

Recommendations

12. Magnesium sulfate is recommended for the prevention of eclampsia in women with severe pre-eclampsia in preference to other anticonvulsants. (High-quality evidence, Strong recommendation)
13. Magnesium sulfate is recommended for the treatment of women with eclampsia in preference to other anticonvulsants. (Moderate-quality evidence, Strong recommendation)
14. The full intravenous or intramuscular magnesium sulfate regimens are recommended for the prevention and treatment of eclampsia. (Moderate-quality evidence, Strong recommendation)
15. For settings where it is not possible to administer the full magnesium sulfate regimen, the use of magnesium sulfate loading dose followed by immediate transfer to a higher level health-care facility is recommended for women with severe pre-eclampsia and eclampsia. (Very-low-quality evidence, Weak recommendation)

Remarks

a. Magnesium sulfate is a lifesaving drug and should be available in all health-care facilities throughout the health system. The guideline development group believed that capacity for clinical surveillance of women and administration of calcium gluconate were essential components of the package of services for the delivery of magnesium sulfate.
b. Clinical evidence supports the use of magnesium sulfate in all pre-eclampsia patients. In settings where there are resource constraints to manage the administration of magnesium sulfate safely in all women with pre-eclampsia, there may be a need to accord greater priority to the more severe cases. Magnesium sulfate is effective in preventing seizures in both mild and severe pre-eclampsia. However, the guideline development group noted that a higher number of women need to be treated to prevent one seizure. The group agreed on the need to treat women with severe pre-eclampsia, but the group members were divided on the use of magnesium sulfate as a prophylaxis for mild pre-eclampsia.
c. Large trials have evaluated and demonstrated the effectiveness of full regimens of magnesium sulfate, which include a loading dose followed by 24-hour maintenance therapy. Specific guidance on how to administer magnesium sulfate can be found in the WHO manual entitled *Managing complications in pregnancy and childbirth: a guide for midwives and doctors*.
d. The guideline development group deliberated on the best course of action in settings in which it is not possible to administer the full magnesium sulfate regimen. The group debated the possible (but yet unproven) benefits of administering only the loading dose versus transferring women with severe pre-eclampsia and eclampsia without any magnesium sulfate. The group felt that that, even in cases where immediate transfer of the woman to a higher-level facility was not possible, the patient was likely to be better off with only the loading dose than without it. The group felt that since this was a common scenario in many low-income countries, it should be given high priority for further research.

Corticosteroids for HELLP (haemolysis, elevated liver enzymes, low platelet count) Syndrome

Recommendation

16. The use of corticosteroids for the specific purpose of treating women with HELLP syndrome is not recommended. (Very-low-quality evidence, Weak recommendation)

Remarks

a. The guideline development group noted that, in addition to the existing evidence, three small trials addressing this research question had been registered in the WHO International Clinical Trials Registry Platform. In one trial (66 women) recruitment had been completed, in the second trial it was still ongoing (160 women) and in the third recruitment was yet to begin. In view of the very low quality of the evidence base on this topic and relative ease of use and availability/affordability of corticosteroids, the group accorded corticosteroids for the treatment of HELLP syndrome high priority for further research.
b. The guideline development group emphasized that the use of corticosteroids for other indications, such as fetal lung maturation, are not included in the above recommendation.

Interventionist versus Expectant Care for Severe Pre-eclampsia before Term

Recommendations

17. Induction of labour is recommended for women with severe pre-eclampsia at a gestational age when the fetus is not viable or unlikely to achieve viability within one or two weeks. (Very-low-quality evidence, Strong recommendation)
18. In women with severe pre-eclampsia, a viable fetus, and before 34 weeks of gestation, a policy of expectant management is recommended, provided that uncontrolled maternal hypertension, increasing maternal organ dysfunction or fetal distress are absent and can be monitored. (Very-low-quality evidence, Weak recommendation)
19. In women with severe pre-eclampsia, a viable fetus and between 34 and 36 (plus 6 days) weeks of gestation, a policy of expectant management may be recommended, provided that uncontrolled maternal hypertension, increasing maternal organ dysfunction or fetal distress are absent and can be monitored. (Very-low-quality evidence, Weak recommendation)

Remarks

a. A policy of expectant management usually includes intra-hospital care with steroids for fetal lung maturation, magnesium sulfate (as necessary), antihypertensive drugs (as necessary), and close maternal and fetal monitoring to identify indications for delivery (e.g., uncontrolled hypertension, deterioration in the condition of the mother and the fetus, including organ dysfunction and fetal distress). As part of expectant management, in-utero transfer to a tertiary-level centre with neonatal intensive care capacity should be considered. The decision on the route of delivery should be made on a case-by-case basis, taking into account, among other factors, gestational age, fetal and cervical status, and urgency.
b. The guideline development group considered that the gestational age threshold for using expectant management in very preterm fetuses depends on the fetal viability status and on the anticipated prolongation of gestation with expectant management. The guideline development group acknowledged that the gestational age threshold of fetal viability should be locally agreed. In establishing this, the local context, the availability of resources, and the local newborn survival rates by gestational age, should be considered. The average gain in terms of prolongation of gestation with expectant management ranges from 1 week to 2 weeks. Hence, fetuses at a gestational age 1–2 weeks below the fetal viability threshold may benefit from expectant management.
c. The guideline development group considered that there was not enough evidence to make a clear-cut recommendation for women with severe pre-eclampsia between 34 and 36 (plus 6 days) weeks of gestation. However, considering the long-term adverse consequences of late preterm birth, the group put more emphasis on expectant management than early delivery.

Induction of Labour for Pre-eclampsia at Term

Recommendations

20. In women with severe pre-eclampsia at term, a policy of early delivery is recommended. (Low-quality evidence, Strong recommendation)
21. In women with mild pre-eclampsia or gestational hypertension at term, induction of labour is recommended. (Moderate-quality evidence, Weak recommendation)

Remarks

a. The guideline development group considered that there is absence of clinical uncertainty over whether termination of pregnancy in women with severe pre-eclampsia at term is beneficial. Quality of evidence provided by the Hypitat trial further downgraded for indirectness.
b. The guideline development group considered that, in women with pre-eclampsia at term, expectant management is associated with a substantial risk of further maternal and fetal complications and absence of substantial maternal and fetal benefits.
c. In settings where gestational age is difficult to determine accurately, special attention should be paid to avoid iatrogenic prematurity in infants.
d. The guideline development group considered that, if induction of labour is contraindicated due to maternal or fetal conditions, early delivery by caesarean section is recommended (as opposed to expectant management).

Prevention and Treatment of Postpartum Hypertension

Recommendations

22. In women treated with antihypertensive drugs antenatally, continued antihypertensive treatment postpartum is recommended. (Very-low-quality evidence, Strong recommendation)
23. Treatment with antihypertensive drugs is recommended for severe postpartum hypertension. (Very-low-quality evidence, Strong recommendation)

Remarks

a. The guideline development group recognized the need for discharge instructions, including education concerning the signs and symptoms associated with postpartum hypertension.
b. In women receiving postpartum antihypertensive treatment, at the present time it is not known at what point the treatment and monitoring of hypertension could be stopped. Hence, the group highlighted this topic as a research priority.
c. The guideline development group put more emphasis on the frequency of postpartum deaths related to stroke and recognized that the maximum increase in blood pressure usually occurs towards the end of the first postpartum week (when, in most settings, women have been already discharged from facility care).
d. In women diagnosed with mild pre-eclampsia antenatally, but not treated with antihypertensive drugs, the initiation of antihypertensive treatment postpartum should be considered for minimizing the risk of complications of severe high blood pressure (see remark 'c' above). That remark was made based on expert opinion and considering the evidence related to the treatment of mild/moderate hypertension during pregnancy. In the postpartum period, the maternal risk of a complication of hypertension is not counterbalanced by the risk of an adverse fetal effect produced by maternal hypotension.
e. The guideline development group considered that there is little clinical uncertainty over whether treatment of severe postpartum hypertension is beneficial. This recommendation was made based on expert opinion and the guideline development group considered that most maternal deaths related to hypertensive disorders are associated with complications of uncontrolled severe high blood pressure. Based on that, the guideline development group agreed that antihypertensive treatment should be recommended in all cases of severe acute hypertension.

Definitions:

Quality of Evidence

Grade	Definition
High	Further research is very unlikely to change confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
Very low	Any estimate of effect is very uncertain

Strength of the Recommendations

The strength of each recommendation was determined during the Technical Consultation using Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology. By default, the strength of the recommendations was initially aligned with the quality of the evidence (i.e., moderate and high quality of evidence prompted strong recommendations while low and very low quality of evidence prompted weak recommendations).

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

- Pre-eclampsia
- Eclampsia
- Postpartum hypertension
- Labour in the presence of pre-eclampsia
- HELLP (haemolysis, elevated liver enzymes, low platelet count) syndrome

Guideline Category

Management

Prevention

Risk Assessment

Treatment

Clinical Specialty

Family Practice

Internal Medicine

Nursing

Obstetrics and Gynecology

Preventive Medicine

Intended Users

Advanced Practice Nurses

Health Care Providers

Nurses

Physician Assistants

Physicians

Public Health Departments

Guideline Objective(s)

- To improve the quality of care and outcomes for pregnant women presenting with pre-eclampsia and its main complications (e.g., eclampsia)
- To present evidence-informed recommendations with a view to promoting the best possible clinical practices for the management of pre-eclampsia and eclampsia

Target Population

Women with or at risk for pre-eclampsia, eclampsia, and hypertensive disorders of pregnancy

Interventions and Practices Considered

1. Calcium supplementation
2. Low-dose acetylsalicylic acid
3. Antihypertensive drugs
4. Magnesium sulfate
5. Induction of labour (as indicated)
6. Postpartum antihypertensive treatment

Note: The following were considered but not recommended: resting at home; dietary salt restriction; diuretics; corticosteroids (for haemolysis, elevated liver enzymes, low platelet count syndrome); and vitamin D, vitamin C and vitamin E supplementation.

Major Outcomes Considered

- Maternal death
- Eclampsia
- Recurrent seizures
- Severe maternal morbidity
- Perinatal deaths
- Adverse effects of interventions
- Admission to neonatal intensive care unit/special nursery
- Apgar scores

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Cochrane systematic reviews of randomized controlled trials (RCTs) were the primary source of evidence for the recommendations. Based on the list of selected questions and outcomes, the guideline steering group identified the relevant Cochrane systematic reviews and determined whether they needed to be updated. Relevant and possibly relevant Cochrane systematic reviews were updated using their specific standard search strategies. A review was considered to be outdated if the last date of search for new trials was two years old, or if there were relevant studies awaiting assessment, as identified by the standard search procedures of the Cochrane Pregnancy and Childbirth Group. For the outdated reviews, the corresponding review authors were invited to update them. Not all authors were in a position to do that within the set deadline. Hence, the review authors who could comply with the deadline and members of the guideline steering group updated the systematic reviews. The search strategies employed to identify the trials and the specific criteria for inclusion and exclusion of the trials are described in the individual systematic reviews.

Number of Source Documents

A total of 19 systematic reviews (including 17 Cochrane systematic reviews) were identified for providing the evidence related to the selected priority questions.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Quality of Evidence

Grade	Definition
High	Further research is very unlikely to change confidence in the estimate of effect.

Grade	Definition
Moderate	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
Very low	Any estimate of effect is very uncertain

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

The following procedures were used to process in a consistent manner each systematic review used to extract the evidence for these guidelines. First, the up-to-date Review Manager software (RevMan) file was retrieved from the Cochrane Pregnancy and Childbirth Cochrane Group. Next, the RevMan file was customized in order to reflect the critical comparisons and outcomes (comparisons and outcomes not relevant to the guidelines were excluded). The next step was to export the RevMan file to the Grading of Recommendations, Assessment and Evaluation (GRADE) profiler software and apply the GRADE criteria for critical appraisal to the retrieved scientific evidence.

As a final step, evidence profiles (GRADE tables) were prepared for each comparison. An online content management system, the Guideline development, Research priorities, Evidence synthesis, Applicability of evidence, Transfer of knowledge (GREAT) project Guideline Production System, was used to handle and share the electronic files.

The standardized criteria used in grading the evidence and the GRADE tables are not included in the guideline document (although table numbers – prefixed with 'EB'– are included for ease of reference): they are published online separately in a document entitled *WHO recommendations for pre-eclampsia and eclampsia: evidence base* (see the "Availability of Companion Documents" field). Each GRADE table relates to one specific question or comparison. The evidence presented in the GRADE tables was derived from a larger body of data extracted primarily from Cochrane reviews, which in many cases contained multiple comparisons (EB Tables 1 to 53 in the evidence base companion document [see the "Availability of Companion Documents" field]). In some GRADE tables data are not presented for all critical outcomes. This is because data for those outcomes were not available in the Cochrane reviews. The raw data which constitute the basis of the GRADE tables are also not included in the guideline document, but can be made available upon request to researchers interested in finding out how the GRADE tables were constructed.

Methods Used to Formulate the Recommendations

Balance Sheets

Expert Consensus

Expert Consensus (Consensus Development Conference)

Description of Methods Used to Formulate the Recommendations

The present guidelines represent the World Health Organization's (WHO's) normative work to support the use of evidence-informed policies and practices in all countries. They form part of the knowledge-to-action project entitled GREAT (Guideline development, Research priorities, Evidence synthesis, Applicability of evidence, Transfer of knowledge) and were developed through standardized operating procedures in accordance with the process described in the *WHO Handbook for guideline development* (see the "Availability of Companion Documents" field). In summary, the process included: (i) identification of critical questions and critical outcomes; (ii) retrieval of the evidence; (iii) assessment and synthesis of the evidence; (iv) formulation of recommendations; and (v) planning for dissemination, implementation, impact evaluation and updating.

First, a guideline steering group was constituted, which included staff of the WHO Departments of Reproductive Health and Research, Making Pregnancy Safer, and Nutrition for Health and Development, and two external experts. This group drafted a list of questions and outcomes related to the prevention and treatment of pre-eclampsia and eclampsia. Next, via an online survey, WHO consulted a group of international stakeholders

(midwives, obstetricians, neonatologists, researchers, experts in research synthesis, experts in health-care programmes, and consumer representatives) to review and prioritize the draft questions and outcomes (first online consultation). The international stakeholders commented on the importance of the drafted questions and outcomes and rated them on a scale of 1 to 9. In this context, a 'critical question or outcome' was defined as a question or outcome that received an average score of 7 or more. Questions and outcomes that scored between 4 and 6 were considered 'important but not critical', while those that scored less than 4 were not considered to be important for the purposes of these guidelines. The international stakeholders were encouraged to revise the questions or suggest new questions and outcomes. The responses to the online survey were reviewed by the guideline steering group. The questions and outcomes rated as critical were included in the scope of this document for evidence grading and formulation of recommendations and were further refined in order to make them conform to the PICO format (population, interventions, comparisons, and outcomes). The average scores given to outcomes by international stakeholders and external experts during the online consultation are presented in Annex 2 of the original guideline document.

The guideline steering group used the information presented in the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tables to draft the recommendations. Balance worksheets were used to summarize the values, preferences and judgements made with regard to the strength of the recommendations. Those balance worksheets are presented in the evidence base document (EB Tables 54–59) (see the "Availability of Companion Documents" field).

In order to review and finalize the draft recommendations and the supporting evidence (including GRADE tables), a preliminary online consultation was held. The draft document and recommendations were made available to a large number of international stakeholders; their opinion was collected via e-mail and through an online survey. This preliminary online consultation was followed by a meeting held in Geneva, Switzerland, on 7–8 April 2011 (WHO Technical Consultation on the Prevention and Treatment of Pre-eclampsia and Eclampsia). A subset of the international group of experts that had participated in the online consultations and other experts were invited to participate in this technical meeting. The draft recommendations and supporting documents were provided to the Technical Consultation participants in advance of the meeting.

Decision-Making During the Technical Consultation

It was planned that the participants in the Technical Consultation would discuss each of the recommendations drafted by the guideline steering group and arrived at a consensus, which was defined as agreement by the large majority of the participants (three quarters of participants), provided that those who disagreed did not feel strongly about their position. Strong disagreements would be recorded as such in the guidelines. The participants had been unable to reach a consensus, the disputed recommendation, or any other decision, would be put to a vote. The recommendation or decision would stand if a simple majority (more than half) of the participants voted for it, unless the disagreement related to a safety concern, in which case the WHO Secretariat would choose not to issue a recommendation at all. WHO staff present at the meeting and other external technical experts involved in the collection and grading of the evidence were not allowed to vote. If the issue to be voted upon involved primary research or systematic reviews conducted by any of the participants who have declared an academic conflict of interest, the participants in question were allowed to participate in the discussion, but were not allowed to vote on it. In addition to the scientific evidence and its quality, applicability issues, costs and other judgements were taken into consideration in the formulation of the final recommendations.

During the meeting, the participants' values and preferences, the magnitude of effect, balance of benefits versus disadvantages, resource use and feasibility of each recommendation were considered. Balance worksheets were used to note and synthesize these considerations (EB Tables 54–59) (see the "Availability of Companion Documents" field) and whenever the default strength of the recommendation was changed due to values and preferences, the reasons were recorded in the balance worksheets.

Rating Scheme for the Strength of the Recommendations

The strength of each recommendation was determined during the Technical Consultation using Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology. By default, the strength of the recommendations was initially aligned with the quality of the evidence (i.e., moderate and high quality of evidence prompted strong recommendations while low and very low quality of evidence prompted weak recommendations).

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

A template for guideline reporting was developed for the World Health Organization's Guideline development, Research priorities, Evidence synthesis, Applicability of evidence, Transfer of knowledge (WHO GREAT) project series of guidelines. That guideline template was used in the preparation of this document. Prior to the Technical Consultation, the guideline steering group prepared a preliminary version of this document, including draft recommendations.

The participants of the Technical Consultation meeting held in Geneva received the draft guidelines and supporting documents 10 days before the meeting. The draft guidelines were also sent to a large number of international stakeholders for peer review together with an online questionnaire about the draft recommendations (preliminary online consultation). Inputs received from the peer reviewers were carefully evaluated by the guideline steering group and the suggestions considered as relevant were included in the document or highlighted for further discussion during the meeting. The guideline steering group refrained from making any substantive changes to the scoping (e.g., further expansion of the guideline scoping) of the guidelines. The comments and feedback received during the preliminary online consultation were discussed during the meeting and incorporated into the document as appropriate. During the meeting, the draft guidelines were modified in line with the participants' deliberations and considering the input of received during the online preliminary consultation. After the meeting, members of the guideline steering group worked on the preliminary version to ensure that a revised version reflected accurately the deliberations and decisions of the participants. The revised version was sent electronically back to the participants in the Technical Consultation for their approval.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Prevention of and appropriate treatment of pre-eclampsia and eclampsia to improve maternal and perinatal mortality and morbidity

Potential Harms

Side effects of antihypertensive medications, including severe maternal hypotension that may adversely affect the fetus

Qualifying Statements

Qualifying Statements

- The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city, or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.
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- These guidelines are not intended as a comprehensive guide on the management of pre-eclampsia and eclampsia.

Implementation of the Guideline

Description of Implementation Strategy

Dissemination and Implementation of the Guidelines

The ultimate goal of these guidelines is to improve the quality of care and health outcomes related to hypertensive disorders of pregnancy. Hence, dissemination and implementation of these guidelines are crucial steps to be undertaken by the international community and local health-care services. The World Health Organization (WHO) Department of Reproductive Health and Research has adopted a formal knowledge-to-action framework for the dissemination, adaptation and implementation of guidelines. In addition to this framework, during the WHO Technical Consultation, a list of priority actions was established which will be used by WHO and other partners to foster the dissemination and implementation of these guidelines:

- Prepare guideline derivatives for policy-makers, consumers, clinicians and other groups (e.g., a two-page policy brief, and a press release for engaging the public via the media. Managing Complications in Pregnancy and Childbirth update).
- Prepare the translation of WHO Executive Summary: three to five pages into six official United Nations languages.
- Seek endorsement by national and international professional societies, including International Federation of Gynecology and Obstetrics, International Confederation of Midwives, and others (e.g., American Congress of Obstetricians and Gynecologists, and Royal College of Obstetricians and Gynaecologists).
- Promote discussion, dissemination and uptake during the International Society for the Study of Hypertension in Pregnancy World Congress in Geneva, 2012.
- Foster agreement between guidelines for unified recommendations.
- Promote the development of local guidelines/protocols based on these guidelines.
- Continue working with the Norwegian Knowledge Centre for developing tools to facilitate the formulation of health policies based on evidence-based guidelines.
- Prepare health system interventions including advocacy actions, "Health Systems Taskforce" and "use of evidence in policy-making" (e.g., EVIPNet [Evidence-Informed Policy Network]).
- Further understand facility processes and develop strategies for behaviour change and guideline uptake.
- Engage local opinion leaders early in the process/explore the use of multifaceted approaches.
- Foster the implementation of near-miss criterion-based clinical audits.
- Increase the visibility and availability of WHO guidelines.
- Disseminate WHO guidelines in Health Sector Review meetings.
- Involve education institutions, develop training and pre-service curriculum.
- Disseminate these guidelines using WHO guidance community and Knowledge Gateway to virtual community.
- Prepare WHO–United Nations Population Fund (UNFPA) Joint Statements related to the main recommendations of these guidelines.
- Maximize the dissemination of these guidelines across WHO (regional and country offices).
- Promote active engagement and dialogue rather than passive distribution and action plans.
- Develop appropriate job aids and clinical decision tools (e.g., how to mix magnesium sulfate).
- Foster availability of magnesium sulfate (e.g., Beximco pharmaceuticals product).
- Promote task shifting (including independent use by all care providers skilled in magnesium sulfate use).
- Explore the development of means to capture issues related to the implementation of these guidelines (e.g., through web site or Knowledge Gateway).
- Further develop maternal and newborn outcome indicators that could better inform clinical practice.

Guideline Dissemination

The recommendations in these guidelines will be disseminated through a broad network of international partners, including WHO country and

regional offices, ministries of health, WHO collaborating centres, other United Nations agencies and nongovernmental organizations. They will also be published on the WHO web site and in the WHO Reproductive Health Library, where it will be accompanied by an independent critical appraisal based on the AGREE (Appraisal of Guidelines Research and Evaluation) instrument. In addition, a policy brief aimed at a wide range of policy-makers, programme managers and clinicians will be developed and disseminated through WHO country offices.

Guideline Implementation

The successful introduction into national programmes and health-care services of evidence-based policies related to the prevention and management of pre-eclampsia and eclampsia depends on well-planned and participatory consensus-driven processes of adaptation and implementation. The adaptation and implementation processes may include the development or revision of existing national guidelines or protocols based on this document.

The recommendations contained in the present guidelines should be adapted into a locally appropriate document that can meet the specific needs of each country and health service. In this context, modifications to the recommendations may be limited to weak recommendations and justification for any changes should be made in an explicit and transparent manner.

In addition to that, a set of interventions should be established to ensure that an enabling environment is created for the use of the recommendations (including, for example, the availability of magnesium sulfate), and that the behaviour of the health-care practitioner changes towards the use evidence-based practices. In this process, the role of local professional societies is important and an all-inclusive and participatory process should be encouraged. The WHO Department of Reproductive Health and Research has published specific guidance on the introduction of WHO's reproductive health guidelines and tools into national programmes.

Refer to Section 7 of the original guideline document for "Applicability Issues," including anticipated impact on the organization of care and resources and monitoring and evaluating the guideline implementation.

Implementation Tools

Audit Criteria/Indicators

Quick Reference Guides/Physician Guides

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Staying Healthy

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

World Health Organization (WHO). WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia. Geneva

(Switzerland): World Health Organization (WHO); 2011. 38 p. [34 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2011

Guideline Developer(s)

World Health Organization - International Agency

Source(s) of Funding

World Health Organization

The University of British Columbia (PRE-EMPT project, a grantee of the Bill & Melinda Gates Foundation) provided additional financial support to the work on these guidelines.

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Guideline Steering Group

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Financial Disclosures/Conflicts of Interest

According to the World Health Organization (WHO) rules, all experts participating in WHO meetings must declare any interest relevant to the meeting prior to their participation. All guideline group members and participants of the meeting completed a Declaration of Interest Form before the meeting. These declarations of interest forms were reviewed by the WHO steering group in consultation with the WHO Legal Department before finalization of the group composition and invitation to attend the guideline group meeting. Box 1 (Annex 1 of the original guideline document) summarizes relevant declarations of interest. In addition, the external advisers verbally declared potential conflicts of interest at the beginning of the meeting. The procedures for management of conflicts of interests strictly followed the *WHO Guidelines for declaration of interest (WHO experts)*. Full participation of all experts was deemed appropriate.

Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available from the World Health Organization Web site .

Print copies: Available from the WHO Press, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland; Phone: +41 22 791 3264; Fax: +41 22 791 4857; E-mail: bookorders@who.int.

Availability of Companion Documents

The following are available:

- WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia. Evidence base. Geneva (Switzerland): World Health Organization (WHO); 2011. 82 p. Electronic copies: Available in Portable Document Format (PDF) from the World Health Organization (WHO) Web site .
- WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia. Summary of recommendations. Geneva (Switzerland): World Health Organization (WHO); 2011. 4 p. Electronic copies: Available in PDF from the WHO Web site .
- World Health Organization. WHO Handbook for guideline development. Geneva (Switzerland): World Health Organization (WHO); 2010. 67 p. Electronic copies: Available in PDF from the WHO Web site .

In addition, a process indicator can be found in section 7 of the original guideline document .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on March 22, 2013. This summary was updated by ECRI Institute on July 12, 2013 following the U.S. Food and Drug Administration advisory on Magnesium Sulfate.

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